Safety of Growth Hormone Treatment in Pediatric Patients with Idiopathic Short Stature

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Context: Recombinant human GH was approved by the United States Food and Drug Administration in 2003 for the treatment of idiopathic short stature (ISS). However, to date, the safety of GH in this patient population has not been rigorously studied.

Objective: The objective of this study was to address the safety of GH treatment in children with ISS compared with GH safety in patient populations for which GH has been approved previously: Turner syndrome (TS) and GH deficiency (GHD).

Design/Setting: The rates of serious adverse events (SAEs) and adverse events (AEs) of particular relevance to GH-treated populations were compared across the three patient populations among five multicenter GH registration studies.

Patients: Children with ISS, TS, or GHD were studied.

Intervention: Treatment consisted of GH doses ranging from 0.18–0.37 mg/kg·wk.

Main Outcome Measures: The main outcome measures were rates of SAEs and AEs of special relevance to patients receiving GH. Laboratory measures of carbohydrate metabolism were used as outcome measures for the ISS studies.

Results: Within the ISS studies, comprising one double-blind, placebo-controlled study and one open-label, dose-response study, SAEs (mainly hospitalizations for accidental injury or acute illness unrelated to GH exposure) were reported for 13–14% of GH-treated patients. Overall AE rates (serious and nonserious) as well as rates of potentially GH-related AEs were similar in the GHD, TS, and ISS studies (for ISS studies combined: otitis media, 8%; scoliosis, 3%; hypothyroidism, 0.7%; changes in carbohydrate metabolism, 0.7%; hypertension, 0.4%). Measures of carbohydrate metabolism were not affected by GH treatment in patients with ISS. There was no significant GH effect on fasting blood glucose in either study (GH dose range, 0.22–0.37 mg/kg·wk) or on insulin sensitivity (placebo-controlled study only).

Conclusion: GH appears safe in ISS; however, the studies were not powered to assess the frequency of rare GH-related events, and longer-term follow-up studies of GH-treated patients with ISS are warranted.

RECOMBINANT HUMAN GH was first approved by the United States Food and Drug Administration (FDA) in 1985 for children with growth failure due to GH deficiency (GHD). Since then, GH has been approved for children with short stature or growth failure in five other disorders that are generally not associated with deficiency of endogenous GH production: chronic renal insufficiency, Turner syndrome (TS), Prader-Willi syndrome, children born small for gestational age, and, most recently, idiopathic short stature (ISS) or non-GH-deficient short stature. Since its initial FDA approval, an estimated 200,000 patients have received GH treatment, representing at least 500,000 patient-years of exposure. During this time, a number of adverse events (AEs) have been well characterized, ranging from relatively common minor disturbances, such as edema and injection site reactions, to more significant, but fortunately rare, events, such as benign intracranial hypertension and slipped capital femoral epiphysis. However, GH is considered overall to be safe for treatment of patients with conditions for which it has been previously approved (1).

The efficacy results from the randomized studies that led to the 2003 approval of GH treatment for short stature in children for whom no underlying cause of the growth disorder can be found, commonly referred to as ISS, have been reported (2, 3). However, to date, most of the published data on the safety of GH treatment in ISS derive from large postmarketing research programs. These observational studies have reported safety data for approximately 9,000 patients with ISS, representing approximately 27,000 patient-years of GH exposure. Overall, AE rates for these patients with ISS were similar to or, in some cases, lower than AE rates for patients with other GH-treated conditions (4, 5). For example, patients with ISS comprised 17.1% of the total National

Abbreviations: Ab, Antibody; AE, adverse event; GHb, glycosylated hemoglobin; GHD, GH deficiency; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; ISS, idiopathic short stature; LDL, low-density lipoprotein; QUICKI, Quantitative Insulin Sensitivity Check Index; SAE, serious AE; SDS, SD score; TFT, thyroid function test; TIW, three times weekly; TS, Turner syndrome.

Cooperative Growth Study population, but accounted for only 4.6% of all serious AEs and 3.4% of deaths, the fewest of any of the patient populations (4). Similarly, patients with ISS had the overall lowest AE rate of all patient groups examined in the Kabi International Growth Study (5).

This report provides safety data from the two randomized registration studies in patients with ISS that formed the basis of the FDA approval for GH treatment of this form of short stature. To provide a perspective of GH safety in ISS relative to other patient groups for whom GH treatment is well established, these data are compared with the AE data derived from registration studies of GHD and TS.

Subjects and Methods

A summary of the design and key features of the five multicenter studies included in this analysis, two in patients with ISS (studies ISS1 and ISS2), one in patients with GHD (study GHD), and two in patients with TS (studies TS1 and TS2), is provided in Table 1. Each protocol was approved by the appropriate institutional or ethics review board(s), and informed consent was obtained from a parent or legal guardian before any study-related procedure was conducted.

GH (Humatrope) was provided by Eli Lilly and Co. (Indianapolis, IN) at doses ranging from 0.18 mg/kg·wk (study GHD) to 0.37 mg/kg·wk (study ISS2). In all studies, patients were excluded if at baseline they had clinically significant cardiac, pulmonary, gastrointestinal, hepatic, or renal disease; diabetes mellitus; active chronic infection; active malignancy; or untreated thyroid dysfunction, or were currently taking amphetamines (for attention disorder) or any other drug suspected to interfere with GH secretion or action. Additional major inclusion and exclusion criteria are provided in Table 1. For all studies, all untoward medical events were reported as AEs in the manner typical of registration studies, regardless of known or suspected relationship to treatment. Standard laboratory evaluations, including blood chemistry, hematology, and urinalysis, were reviewed locally by the investigators in each study and are not reported here. Specific laboratory evaluations most relevant to patients receiving GH are described below. Because this report focuses on GH safety in patients with ISS and because assays and methodologies differed among studies, laboratory data are reported only for the ISS studies.

Within-study, between-group differences (*e.g.* ISS1, GH *vs.* control) in AE frequencies were analyzed by Fisher exact test. Statistical comparisons of AE rates among the different studies were not performed,

TABLE 1. Clinical studies included in safety comparison

Study	ISS1	ISS2	GHD	TS1	TS2
Patient population	ISS	ISS	GHD	TS	TS
Location (no. of study sites)	United States (2)	Europe (28)	United States (67)	Canada (14)	United States (50)
Design	Double-blind, randomized, parallel, placebo-controlled	Open-label, randomized, parallel, 3-arm, dose response	Open label, single-arm	Open-label, randomized, parallel, untreated control	Double-blind, randomized, parallel, dose response (placebo-controlled for first 1.5 yr)
End point	Final height	2-yr height velocity; extension to final height	1-yr height velocity; extension to final height	Final height	18-mo height velocity; extension to final height
No. in safety analysis	68	239	333	136	230
No. GH-treated	37	239	333	74	230
GH dose (mg/kg·wk)	0 (placebo) 0.22	0.24 0.24→0.37[b] 0.37	0.18–0.24[a]	0 (control) 0.30	0.27 0.36
Duration (yr)	Placebo: 3.3 ± 1.6 GH: 3.7 ± 1.9	0.24: 4.7 ± 2.4 0.24→0.37: 4.4 ± 2.4 0.37: 4.5 ± 2.4	3.7 ± 2.7	Control: 3.7 ± 1.6 GH: 4.1 ± 1.5	0.27: 4.1 ± 2.1 0.36: 4.5 ± 2.2
Entry criteria[c]					
Sex	M and F	M and F	M and F	F	F
Age (yr)	10–16 M; 9–15 F	≥5	≥2	7–12	≥5
Bone age (yr)	≤13 M; ≤11 F	<12 M; <10 F	≤11 M; ≤12 F	Not specified	≤12
Height[d]	≤−2.25 SDS	≤−2.0 SDS	Not specified	<10th percentile	Not specified
Height velocity[d]	Not specified	<25th percentile	<3rd percentile	<6 cm/yr	<6 cm/yr
Pubertal status	Tanner 1 or 2	Tanner 1	Tanner 1	Tanner 1	Tanner 1
Peak GH response	>7 μg/liter	>20 mU/liter (~10 μg/liter)	<10 μg/liter	≥8 μg/liter	Not specified
Other requirements	Normal karyotype; no history of CNS trauma or surgery	No organic cause of growth failure, primary bone disease, endocrine or metabolic disorder, or dysmorphic syndrome	Isolated GH deficiency or panhypopituitarism; normal karyotype (F)	Gonadectomy if any Y chromosomal material in karyotype	No Y chromosomal component in karyotype

CNS, Central nervous system; F, female; M, male; mo, months. Notes regarding inclusion/exclusion criteria: All studies required that thyroid and adrenal function be normal or appropriately replaced and that patients not have been exposed to treatment with GH. Studies ISS1, TS1, and TS2 required that patients not have been exposed to androgens, estrogens, or pharmacological doses of glucocorticoids. Studies ISS1, GHD, TS1, and TS2 required that patients not have received chemotherapy or radiation for malignancy (study ISS1, within the previous 5 yr). Patients were excluded if they had a history of malignancy in studies GHD (within the previous 2 yr), TS1, and TS2.

[a] Patients received 0.18 mg/kg·wk GH initially, then up to 0.24 mg/kg·wk GH based on clinical response.

[b] Patients received 0.24 mg/kg·wk GH for the first year and 0.37 mg/kg·wk GH thereafter.

[c] Critical inclusion/exclusion criteria are provided.

[d] All height and height velocity percentiles or SDS are calculated according to age and sex.

because this analysis was performed *post hoc*, and the studies were not designed for such analyses. Between-group comparisons of laboratory values were performed by ANOVA. Between-group differences with $P \leq 0.05$ (two-sided) were considered significant. Data are expressed as mean ± SD unless otherwise stated.

Study ISS1

In this double-blind, placebo-controlled study, 71 patients (55 males and 16 females) were randomly assigned to receive either 0.22 mg/kg·wk GH (n = 38) or placebo (n = 33), administered in divided doses by sc injection three times weekly (TIW). Safety data are provided for the 68 patients who received at least a single injection.

For safety analyses, blood was drawn while subjects were fasting at study entry and every 6 months thereafter for glucose, insulin, glycosylated hemoglobin (GHb) or hemoglobin A_{1c} (HbA_{1c}; after 1998), lipid profile, IGF-I, thyroid function tests (TFTs; total and free T_4, T_3, and TSH), GH antibodies (Ab), and anti-*Escherichia coli* Ab. Insulin sensitivity was estimated using the Quantitative Insulin Sensitivity Check Index (QUICKI), calculated as $1/(\log_{10}[\text{fasting insulin } (\mu U/ml)] + \log_{10}[\text{fasting glucose (mg/dl)}])$ (6). Mean fasting glucose and insulin levels have been reported previously (2), as have TFTs for a subset of patients (7).

Study ISS2

In this multicenter, dose-response study, 239 patients (158 males and 81 females) were randomly assigned to one of three GH treatment groups [0.24 mg/kg·wk, n = 78; 0.24 mg/kg·wk for the first year and 0.37 mg/kg·wk thereafter (0.24→0.37 mg/kg·wk), n = 78; or 0.37 mg/kg·wk, n = 83]. GH was administered in divided doses by sc injection six times weekly. Safety data are reported for all randomized patients, including six who discontinued the study before receiving any GH.

Blood was collected fasting at study entry, then at 3, 6, 9, 12, 18, and 24 months, and annually thereafter for glucose, GHb, GH Ab, and *E. coli* Ab. TFTs and IGF-I were measured locally and were not available for centralized analysis.

Study GHD

This open-label, multicenter study enrolled 333 patients (236 males and 97 females) to receive a GH dose of 0.18 mg/kg·wk, divided TIW, with the option of increasing the dose to 0.24 mg/kg·wk based on clinical response. Efficacy data for this study have been reported (8). Safety data are provided for all enrolled patients, including 19 who discontinued the study before receiving any GH.

Study TS1

In this randomized, controlled, multicenter study, 140 girls were assigned to either a GH group (0.30 mg/kg·wk, in divided doses six times weekly; n = 75) or an untreated (no injection) control group (n = 65). After 1 yr on study, patients in both groups who were at least 13 yr of age also received ethinyl estradiol, with addition of medroxyprogesterone acetate 1 yr later for patients at least 15 yr of age. The primary data for this study have been reported (9, 10). Safety data are provided for the 136 patients for whom any postbaseline data were available.

Study TS2

In this multicenter, randomized, controlled, dose-response study, 232 girls were assigned in a double-blind fashion to one of five treatment groups encompassing GH doses of 0.27 mg/kg·wk (two groups) and 0.36 mg/kg·wk (two groups) or placebo (one group), with or without low-dose estradiol at a dose of approximately 100 ng/kg·d across the duration of the study. GH was administered in divided doses TIW for the first 6 yr of the study and six times weekly thereafter. After 18 months on study, the treatment group receiving placebo injections and oral placebo was reassigned to GH (0.36 mg/kg·wk) with oral placebo without unblinding the patients or investigators. Efficacy data for this study have been reported (11).

For the purpose of these safety analyses, patients in the two study groups receiving the GH dose of 0.27 mg/kg·wk with or without estrogen were pooled as a single 0.27-mg dose group, and patients in the three groups receiving the GH dose of 0.36 mg/kg·wk with or without estrogen were pooled as a single 0.36-mg dose group. Safety data are reported for the 230 patients who received at least one dose of GH.

Results

The number of patients and the duration of GH exposure were similar across the three patient populations, with approximately 300 patients receiving treatment for approximately 1200 patient-years in each patient group (Table 2).

AEs

There were few deaths in any of the studies, and none was considered likely to be related to GH treatment. In study ISS2, a 16-yr-old boy died approximately 4 yr after study discontinuation from an abdominal desmoplastic small round cell tumor (details below). There were three deaths in the GHD study: a 6-yr-old boy with cerebral palsy aspirated and died during sleep; a 5-yr-old boy with panhypopituitarism died after respiratory arrest associated with influenza, hypoglycemia, and dehydration; and a 20-yr-old male died from vascular complications during surgery to remove a suprasellar cyst. One untreated control subject in study TS1 died due to a ruptured aortic aneurysm.

There were two reports of neoplasia during the ISS studies, six during the GHD study, and none during the TS studies. In study ISS1, an 11-yr-old boy was diagnosed with stage 3B Hodgkin disease (involvement of lymph nodes on both sides of the diaphragm, accompanied by systemic symptoms) after receiving 0.22 mg/kg·wk GH for 19 wk (2). However, a number of findings suggest the presence of subclinical disease before receiving GH: a prestudy chest x-ray demonstrated a widened mediastinum (a finding characteristic of lymphoma, at the time reported as probably due to a thymus remnant); at study entry (pre-GH), the patient had a high-normal erythrocyte sedimentation rate (32 mm/h; reference range, 1–39 mm/h) and mild elevation of lactic dehydrogenase (248 U/liter; reference range, 113–226 U/liter); by 12 wk on study, the erythrocyte sedimentation rate was clearly elevated (58 mm/h), accompanied by persistent elevation of lactic dehydrogenase (257 U/liter).

In study ISS2, a 12-yr-old boy who had received 0.24 mg/kg·wk GH for 6.4 yr was diagnosed with and subsequently died from an abdominal desmoplastic small round cell tumor (3). The cells of the tumor had an abnormal karyotype, with a chromosomal translocation [46,XY,t(11;22)(p13;q12)] and a duplication of the short arm of chromosome 1.

Neoplastic disorders were reported for six patients in the GHD study. Four cases represented recurrence or progression of intracranial tumors present before study entry. A fifth patient was reported to have a new diagnosis of craniopharyngioma after nearly 3 yr on study; it is not known whether intracranial imaging was performed before study entry. The final case was a papillary carcinoma of the thyroid in a patient with prior history of acute lymphoblastic leukemia treated with chemotherapy, total body irradiation, and bone marrow transplantation.

SAEs (defined by regulatory criteria as those that result in death, hospitalization, life-threatening consequences, severe or permanent disability, cancer, or other significant conse-

TABLE 2. AEs of relevance in GH-treated patients

	Patient population		
	ISS	GHD	TS
No. (total no. in each patient population)	276	333	304
Total patient-years of GH exposure	1212	1232	1219
No. of GH-treated patients with serious AE[a]			
Death[b]	1	3	0
Life-threatening event	0	1[c]	1[d]
Neoplasm	2[e]	6	0
Hospitalization, surgical procedure	15	53	39
Hospitalization, other reason	21	89	33
Other	5[f]	7[g]	9[h]
No. (%) of GH-treated patients with other notable AE[i]			
Otitis media	22 (8.0)	95 (28.5)	133 (43.8)
Scoliosis	8 (2.9)	5 (1.5)	1 (0.3)
Hypothyroidism	2 (0.7)[j]	78 (23.4)	50 (16.4)
Alteration in carbohydrate metabolism	2 (0.7)	1 (0.3)	1 (0.3)
Hypertension	1 (0.4)	1 (0.3)	15 (4.9)
Slipped capital femoral epiphysis	1 (0.4)	1 (0.3)	0 (0.0)
Benign intracranial hypertension	0 (0.0)	1 (0.3)	1 (0.3)
Edema	0 (0.0)	5 (1.5)	6 (2.0)
Prepubertal gynecomastia	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)

[a] Defined by regulatory criteria as those AEs that result in death, hospitalization, life-threatening consequences, severe or permanent disability, cancer, or other significant consequence.
[b] Reported either during or after study participation.
[c] Ventriculoperitoneal shunt revision.
[d] Dyspnea (study TS1).
[e] One of these patients subsequently died from a desmoplastic small round cell tumor after discontinuing study ISS2.
[f] One case of accidental overdose of a nontherapeutic agent and four cases of convulsions (study ISS2).
[g] One case each of arthralgia, hypothyroidism, and injection site hemorrhage; two cases of convulsions; and two cases of accidental overdose.
[h] One case of hypochromic anemia (study TS1); one surgical removal of cholesteatoma, one case of hematuria, and six cases of accidental overdose (study TS2).
[i] Listed in order of descending frequency for total patients in the combined ISS studies.
[j] There were also two reports of hypothyroidism in placebo-treated patients with ISS (6.5%).

quences) were reported for GH-treated patients in each of the studies as follows: ISS1, 14% (and 7% of placebo-treated); ISS2, 13%; GHD, 27%; TS1, 27% (and 13% of controls); and TS2, 5%. As expected in pediatric patient populations, the majority of these events were hospitalizations for accidental injury, surgery, or acute illness (Table 2).

Events of specific relevance to GH safety [either referenced in the product safety information (12) or reported in other GH-treated populations] were evaluated, including alterations in carbohydrate metabolism, hypertension, hypothyroidism, otitis media, scoliosis, slipped capital femoral epiphysis, benign intracranial hypertension, edema, pancreatitis, and prepubertal gynecomastia. There were no reports of the latter four conditions in either of the ISS studies. The rates of the remaining listed AEs for GH-treated patients with ISS were similar to those reported for patients with GHD or TS (Table 2), and no significant differences were observed in the frequencies of these events between the GH- and placebo-treated groups in study ISS1 or among the three GH dose groups in study ISS2.

Disorders of carbohydrate metabolism were reported for two patients with ISS and one patient each with GHD and TS. There were no reports of diabetes mellitus in patients with ISS or GHD; however, type 1 diabetes was reported for one patient in study TS2. Hyperglycemia was reported as an AE for one patient in the GHD study. The two carbohydrate metabolism-related events reported in the ISS studies were both mild and reversible. In study ISS2, a 13-yr-old girl who had received 0.24 mg/kg·wk GH for over 8 yr was reported to have decreased glucose tolerance (3). Although asymptomatic, she had a borderline high HbA_{1c} of 6.1% (upper limit of normal for the laboratory, 6.0%) and a borderline high serum glucose at the 2-h point of an oral glucose tolerance test [11.1 mmol/liter (200 mg/dl); upper limit of normal, 11.0 mmol/liter (198 mg/dl)]. GH was discontinued, and her HbA_{1c} was normal (5.3%) 1 yr later. A second patient in study ISS2 had a single reported instance of hyperglycemia at 6 yr on study [fasting glucose, 7.4 mmol/liter (133 mg/dl); upper limit of normal for the laboratory, 7.0 mmol/liter (126 mg/dl)]. Fasting blood glucose was normal [5.0 mmol/liter (90 mg/dl)] when retested approximately 2 wk later.

Scoliosis, which has been associated with rapid growth (13, 14), was reported more frequently in study ISS1 than in any of the other four studies [seven (19%) GH-treated and four (13%) placebo-treated patients; no significant difference between groups]. In this study (unlike the remaining studies), examination for scoliosis was performed by the forward bend test at each study visit. This test has been reported to have a false positive rate of approximately 57% (15), possibly increasing the diagnosis of mild degrees of the condition, which occurs in 4.5% of the general adolescent population (16). None of the cases was significant enough to require x-ray, and none progressed or required treatment. Scoliosis was reported for a single patient each in studies ISS2 and TS2 and for five patients in study GHD (Table 2).

Slipped capital femoral epiphysis, which has a general

population prevalence of less than 0.01% (17), was reported for one ISS patient and one GHD patient, but no patients with TS. In study ISS2, a 16-yr-old male who had received 0.37 mg/kg·wk GH for more than 5 yr fell during an epileptic seizure and sustained a fractured head of right femur, later diagnosed as slipped capital femoral epiphysis. In the GHD study, an 18-yr-old male (bone age, 13 yr) was hospitalized for surgical repair of slipped capital femoral epiphysis.

As shown in Table 2, otitis media, an extremely common childhood condition, was reported less frequently in the ISS studies (8%) than in the GHD (29%) or TS (44%) studies. On-study development or worsening of hypothyroidism was reported in two patients with ISS (0.7%, both in study ISS2) compared with 23% of GHD patients, 16% of GH-treated patients with TS, and a general population rate in adolescents estimated at 0.1% (18).

Elevated triglycerides were reported for three GH-treated patients and one placebo-treated patient in study ISS1, but were not reported in any of the remaining studies due to differences in testing and reporting practices across the studies. Numerous AEs of a nonserious nature (including many common illnesses, such as rhinitis, pharyngitis, and influenza) were reported for the majority of patients in all treatment groups (GH-treated and control) in each of the five studies, with no evidence of a GH effect. In addition, various aches and pains (myalgia, arthralgia, aching joints, hip pain, and back pain) were reported commonly in all patient groups in all studies.

Laboratory analyses

Because of differences in laboratory methodologies and reporting across the studies, this section reports results only for the ISS studies. No abnormalities were detected on standard chemistry or hematology parameters or on tests for *E. coli* or GH Abs in either ISS study (data not shown). Analyses of relevance to patients receiving GH, including IGF-I, TFTs, and measures of carbohydrate metabolism, are reported below. Data were analyzed at baseline and at every study visit for the mean ± SD and for the proportion of patients in each treatment group whose values fell above or below the limits of the normal range for that analyte. For reasons of space, unless otherwise noted, data are presented only for baseline and for the most extreme value of the mean obtained at any subsequent annual analysis.

IGF-I

IGF-I was assayed at a central laboratory only in study ISS1. Mean baseline IGF-I concentrations were below average for age and sex for both treatment groups [GH, −1.4 ± 1.6 SD score (SDS); placebo, −1.9 ± 1.1 SDS]. Overall, 54% of patients had baseline values below −2 SDS, and 90% had values less than 0 SDS. As expected, the GH-treated group had a significantly greater on-study IGF-I increase than the placebo group (mean change from baseline to last visit: GH, 187 ± 123 ng/ml; placebo, 103 ± 105 ng/ml; $P = 0.007$). The between-group (GH *vs.* placebo) difference in IGF-I SDS values was statistically significant at only the 2 and 5 yr points (2 yr, 0.4 ± 0.4 *vs.* −1.0 ± 0.3 SDS, respectively; 5 yr, −0.4 ± 0.4 *vs.* −1.6 ± 0.3 SDS, respectively; Fig. 1). The majority of patients in both treatment groups had IGF-I values no greater than +2.0 SDS throughout the study, and there was no significant difference between the GH and placebo groups for the proportion of subjects with IGF-I greater than +2.0 SDS

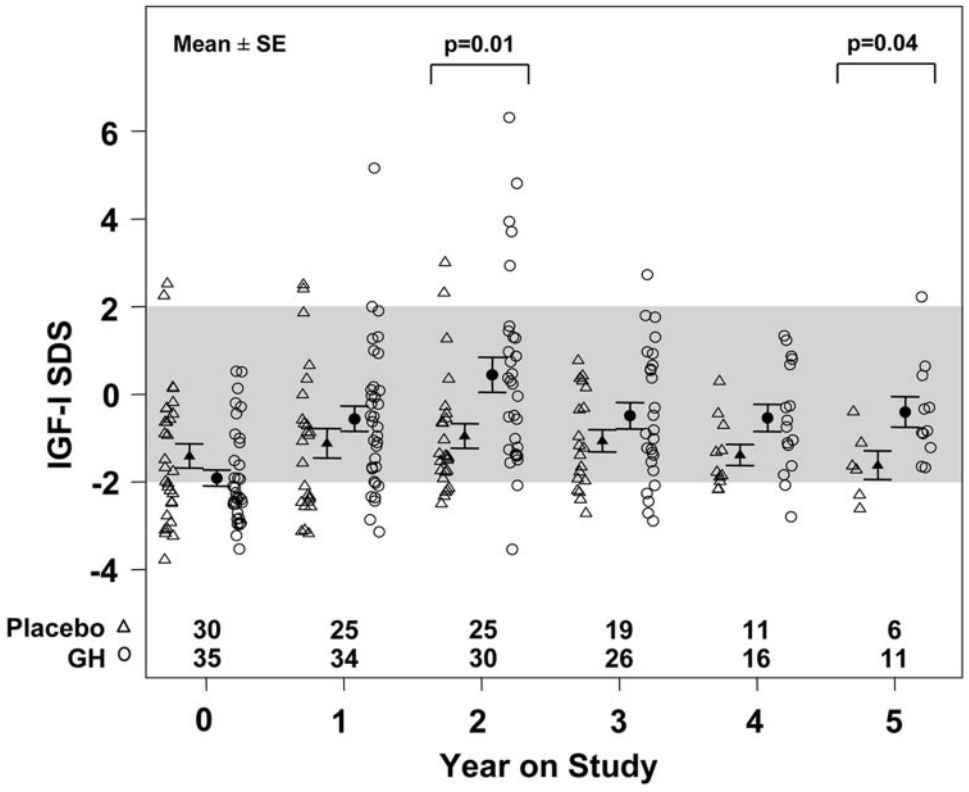

FIG. 1. IGF-I SDS by year on study for study ISS1. Placebo: △, individual patient values; ▲, mean (±SE) values; GH, 0.22 mg/kg·wk: ○, individual patient values; ●, mean (±SE) values. The *shaded area* represents the normal range. The number of patients at each year on study is indicated for each treatment group. Mean IGF-I SDS values were significantly higher for the GH group at 2 and 5 yr on study.

at any postbaseline measurement [GH, nine of 35 subjects (26%); placebo, seven of 28 subjects (25%)].

Measures of carbohydrate metabolism

Fasting blood glucose and HbA_{1c}/GHb. Average fasting blood glucose values measured on an annual basis were similar among the five treatment groups across the two ISS studies. Values were not significantly changed with GH treatment, and no GH dose effect was detected (mean baseline and highest annual values: study ISS1: placebo, 86.9 ± 8.9 and 92.5 ± 8.9 mg/dl; GH, 88.4 ± 6.1 and 92.5 ± 5.9 mg/dl; study ISS2: 024 mg/kg·wk, 82.0 ± 12.9 and 85.0 ± 13.9 mg/dl; 0.24→0.37 mg/kg·wk, 79.6 ± 14.0 and 87.2 ± 13.0 mg/dl; 0.37 mg/kg·wk, 81.2 ± 12.4 and 86.8 ± 18.5 mg/dl). Rare, sporadic elevated blood glucose values were observed for individual patients, probably due to inadequate fasting. As would be expected from the lack of GH effect on fasting blood glucose, no significant changes were observed in HbA_{1c} (study ISS1) or GHb (study ISS2).

Fasting insulin and indices of insulin sensitivity. Analyses of insulin sensitivity were performed only in study ISS1. There were no significant differences in mean fasting insulin between the GH- and placebo-treated groups throughout the study (mean baseline and highest annual values: placebo, 13.8 ± 9.4 and 17.5 ± 9.6 μU/ml; GH, 11.9 ± 8.9 and 16.5 ± 6.3 μU/ml). Nevertheless, because fasting glucose and insulin concentrations may fail to reveal subtle changes in insulin sensitivity, an analysis of the QUICKI, a validated measure of insulin sensitivity, was performed. In this analysis, higher values reflect greater insulin sensitivity. As shown in Fig. 2, there was marked interindividual variation in the pattern of QUICKI changes from baseline to last visit in both treatment groups. Overall, there was no systematic difference between the treatment groups for the pattern of these changes. Furthermore, by analysis of covariance accounting for a slight imbalance in baseline QUICKI values, there was no significant GH effect on the change in QUICKI values from baseline to last visit.

Lipid profiles

Lipid analyses were performed only in study ISS1. No significant differences in mean total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein cholesterol, or triglyceride levels were observed between the GH and placebo groups at any annual time point throughout the study. Both treatment groups had declines (14–23%) in mean values for total cholesterol (placebo, 173.2 ± 25.8 to 149.5 ± 11.0 mg/dl; GH, 177.2 ± 32.5 to 141.1 ± 27.8 mg/dl), HDL cholesterol (placebo, 54.8 ± 11.4 to 47.2 ± 9.9 mg/dl; GH, 55.5 ± 13.2 to 42.6 ± 8.0 mg/dl), and LDL cholesterol (placebo, 104.7 ± 21.6 to 86.1 ± 17.7 mg/dl; GH, 103.8 ± 33.3 to 83.9 ± 23.6 mg/dl) across the duration of the study, probably due to pubertal progression, as previously reported (19–22). However, the ratio of total cholesterol to HDL cholesterol remained essentially unchanged in both groups (placebo, 3.2 ± 0.6 to 3.3 ± 0.7; GH, 3.4 ± 1.0 to 3.5 ± 0.9).

Thyroid function

No GH treatment effects were detected on any measure of thyroid function in study ISS1, as evidenced by similarity at all annual time points between the mean values for GH- and placebo-treated patients for total T_4, free T_4, T_3, and TSH. Both treatment groups had declines (9–21%) in mean total T_4 (mean baseline and lowest values: placebo, 8.0 ± 1.1 to 7.3 ± 1.4 μg/dl; GH, 8.0 ± 1.5 to 6.7 ± 1.1 μg/dl) and T_3 (baseline and lowest values: placebo, 177.5 ± 23.8 to 140.0 ± 27.8 ng/dl; GH, 167.6 ± 22.3 to 131.7 ± 17.3 ng/dl), consistent with the known age-related declines in these hormones. However, there was essentially no change in free T_4 (mean baseline and lowest annual values: placebo, 1.3 ± 0.2 and 1.3 ± 0.2 ng/dl; GH, 1.3 ± 0.2 and 1.2 ± 0.2 ng/dl) or TSH

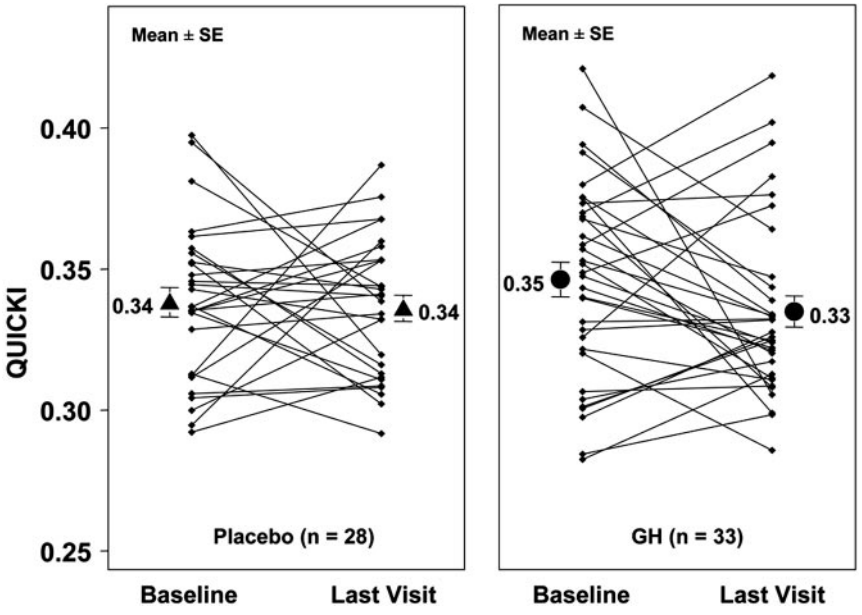

FIG. 2. Study ISS1: QUICKI, calculated as $1/(\log_{10}$ [fasting insulin (μU/ml)] + $\log_{10}$ [fasting glucose (mg/dl)]) (6). Baseline and last visit values are shown for each patient (*small symbols connected by lines*); mean ± SE values are shown by *large symbols*. Higher values indicate greater insulin sensitivity. By analysis of covariance, there was no significant GH effect on the change in QUICKI values from baseline to the last visit.

(mean baseline and highest annual values: placebo, 2.2 ± 1.0 and 2.4 ± 1.4 mU/liter; GH, 2.3 ± 1.3 and 2.3 ± 1.9 mU/liter). TFTs in study ISS2 were performed locally and were not available for this report.

Discussion

Data collected for nearly 60,000 patients during long-term observational studies have demonstrated the general safety of recombinant human GH for the treatment of various pediatric growth disorders (4, 5, 23–26). Included among the numbers of GH-treated patients are more than 9000 with ISS, for whom reported rates of AEs are similar to or lower than the rates for patients with other GH-treated conditions. Nevertheless, the potential influence of GH on carbohydrate metabolism and concerns regarding possible associations among GH, IGF-I, and various neoplastic diseases underscore the need for continued surveillance of the safety of GH treatment (for recent reviews, see Refs. 1 and 27–33).

The data in this report from two long-term randomized trials of GH treatment to final height in patients with ISS are consistent with the extensive observational study evidence of GH safety in this patient group. Furthermore, the present report demonstrates a safety profile for GH treatment in patients with ISS similar to that seen in clinical trials of similar duration and GH exposure in patients with GHD and TS, growth disorders for which GH has been approved for some time and for which a large body of postapproval safety data has been acquired. Specifically, rates of otitis media, scoliosis, slipped capital femoral epiphysis, hypothyroidism, disturbances of carbohydrate metabolism, and hypertension in patients with ISS were similar to or lower than the rates of these conditions in patients with GHD or TS, and no case of benign intracranial hypertension, edema, pancreatitis, or prepubertal gynecomastia was reported in the ISS studies.

Although the overall safety of GH treatment in children with ISS appears similar to that in other pediatric populations, certain aspects of GH action deserve special attention. GH is generally considered to have two major activities: mitogenic effects in stimulating cell proliferation and growth, and anabolic/metabolic effects on protein, carbohydrate, and fat metabolism. Because of the general growth-inducing effect of GH, there has been considerable discussion regarding the potential influence of GH and IGF-I on neoplastic cell growth, and numerous retrospective studies have examined the rates of neoplasia in GH-treated populations. There were two reports of neoplasia during our ISS studies. However, clinical and molecular data suggest no causal association with GH exposure in either case. In the case of the patient with advanced Hodgkin disease diagnosed after 19 wk of GH treatment, a number of findings uncovered retrospectively indicate a strong likelihood that the condition was present, albeit subclinically, before GH exposure. Although a role for GH in the initiation of this patient's Hodgkin disease appears unlikely, GH could conceivably have accelerated the rate of progression of the disease, resulting in earlier clinical presentation.

The second case of neoplasia in the ISS studies, a desmoplastic small round cell tumor diagnosed after 6.4 yr of GH treatment, also appears to have been unrelated to GH exposure, based on the molecular biology of this unusual tumor. Analysis of the tumor tissue revealed the chromosomal translocation typical of this tumor [46,XY,t(11;22)(p13;q12)] (34–37). The break points involve two genes that are associated with other malignant tumors, specifically, Wilms tumor (the *WT1* gene at 11p13) and the Ewing family of primitive neurectodermal tumors (the *EWS* gene at 22q12). This translocation produces a fusion gene comprising the 5′ portion of the *EWS* gene and the 3′ portion of the *WT1* gene (38). The product of this oncogene is a chimeric transcription factor that places the transactivating power of the EWS transcription factor upstream of the gene-targeting zinc-finger region of WT1. This highly oncogenic transcription factor is believed to be responsible for the development of this tumor (38). Review of *in vitro* and *in vivo* data does not suggest a role for GH in generation of the chromosomal translocation event that produced this oncogene (39–44). Furthermore, no other case of desmoplastic small round cell tumor has been reported in the 16 yr of literature on the safety of recombinant human GH. Although neither case of neoplasia in the ISS clinical trials is believed to be causally related to GH exposure, potential associations between GH, IGF-I, and neoplasia underscore the importance of careful evaluation of each malignancy reported in association with GH exposure.

A number of studies have evaluated the risk for *de novo* neoplasia in GH-treated children without previous malignancy (23, 25, 45–47). One retrospective study of 1848 patients treated with cadaveric GH between 1959 and 1985 in Great Britain reported a significant increase in the rate of colorectal cancer (two cases *vs.* the expected 0.25 cases) (47). However, one affected patient may have had familial polyposis coli, a known risk factor for colon cancer. If this case had been excluded from the analysis, the standardized incidence ratio for colon cancer would not have been statistically significant. As these researchers and others (48) have noted, the results were also limited by the small sample size, the form of GH (cadaveric), and the nonphysiological dosing regimen used, and should therefore be interpreted cautiously, without generalization to patients receiving modern dosing regimens of recombinant human GH. Furthermore, a substantially larger report of more than 6000 patients treated between 1963 and 1996 under the auspices of the U.S. National Hormone and Pituitary Program found no increase in the rate of colorectal cancer deaths in GH-treated patients (49). Similarly, other retrospective studies have detected no increase in rates of *de novo* neoplasia in GH-treated children (23, 25, 45, 46). Despite these generally reassuring data, the potential relationship among GH, IGF-I, and neoplasia requires continued vigilance of GH-treated patients. Although only modest increases in serum IGF-I were seen in GH-treated patients in the placebo-controlled ISS study reported here, it should be noted that the GH dose used (0.22 mg/kg·wk) is at the lower end of the spectrum of current GH treatment practice. Higher GH doses could generate IGF-I concentrations that more frequently exceed the physiological range. Consequently, guidance offered by professional societies such as the Lawson Wilkins Pediatric Endocrine Society and the Growth Hormone Research Society, which have recommended monitoring of IGF-I and IGF-binding pro-

tein-3 in patients receiving GH treatment (1, 50) and continued careful surveillance, remains appropriate.

Because of its physiological role in the maintenance of normoglycemia during times of substrate restriction (*e.g.* fasting), via mechanisms such as stimulation of hepatic gluconeogenesis and suppression of insulin-stimulated glucose uptake by peripheral tissues, GH has long been regarded as an insulin antagonist with respect to carbohydrate metabolism. As an extension of this physiological action, supraphysiological GH concentrations may increase glucose production sufficiently to stimulate insulin secretion to maintain normoglycemia. Consequently, there has been significant attention focused on the potential for exogenous GH to induce insulin resistance or even frank diabetes. As would be expected from its physiological mechanism of action, administration of GH to non-GHD children with various growth disorders has been reported to induce increases in fasting insulin; however, insulin concentrations have generally remained within the normal range, and values have returned to baseline after the cessation of GH treatment (51–56). Although certain subgroups of patients, including those with TS, Prader-Willi syndrome, and intrauterine growth retardation, are inherently at greater risk of developing disorders of carbohydrate metabolism (1, 57, 58), most long-term data regarding exacerbation of such problems by GH in these patients have been reassuring (51, 52, 55, 59–61).

Unlike children with other forms of non-GHD short stature, such as those discussed above, children with ISS have no underlying risk for disturbances of carbohydrate metabolism, and thus, assessment of the effects of GH on glucose homeostasis and insulin secretion may be more straightforward in this group. In agreement with a previous report on the metabolic effects of GH treatment in 62 patients with ISS (54), we found no significant GH effect on measures of carbohydrate metabolism in our two studies representing 276 patients with ISS. Although these findings are reassuring, they are limited by the relatively low dose of GH used in the placebo-controlled study (0.22 mg/kg·wk) and the lack of fasting insulin data for the dose-response study. Appropriate caution should therefore be exercised, especially in children with risk factors for type 2 diabetes, such as obesity or a positive family history.

The safety data from these randomized registration studies have several potential limitations. First, the studies may have failed to detect AEs occurring at frequencies of less than one in 400 patient-years, given the size of the study populations and allowing for the confidence intervals for AE frequencies. Second, these studies were not designed to detect potential late events emerging long after completion of GH therapy. These limitations inherent to clinical trials are best addressed through large, longer-term observational studies of patients treated under normal clinical practice conditions. To date, such studies have yielded safety conclusions for ISS similar to those of the two randomized studies reported here (4, 5). Although the data reported in this study and previously suggest no new safety concerns in patients receiving GH treatment for ISS, careful longer-term follow-up is needed.

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